Empagliflozin and diuretics in the elderly: more harm than good?

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Story from the Front Lines

A man in his 60s with longstanding type 2 diabetes complicated by neuropathy, foot osteomyelitis, recurrent falls, CAD and HFpEF presented to his primary physician for a routine visit. His physician noticed his recent A1C of 7.8% on glipizide (metformin allergy) and started empagliflozin for improved glucose management and cardiovascular outcomes. In the months afterwards, he was admitted twice for falls with hypovolemia as a major contributor. During these hospitalizations and subsequent outpatient follow up appointments, his creatinine increased from a baseline of 1.3 with other objective findings consistent with hypovolemia. It was later noticed that the patient had been taking torsemide up to twice a day despite physician instruction to decrease his diuretic frequency. Although it is impossible to establish a causative relationship between empagliflozin and this gentleman's falls requiring multiple admissions; we aim to discuss the risk/benefits of SGLT2 inhibitors and discuss A1C goals in older patients such as ours.

Teachable Moment

The landmark trial investigating empagliflozin in diabetics with CAD found an ARR of 1.6% (NNT 63) over 3 years in the primary outcome of death from cardiovascular diseases, nonfatal MI and nonfatal strokes. Interestingly, the Kaplan-Meier curve for primary outcome had a noticeable difference by 6 months, supporting the notion that empagliflozin's beneficial effects may not be secondary to improved glycemic control. Interestingly, 40% of participants were concurrently taking a diuretic, however the type of diuretic and frequency are not described. The reported hypovolemic event rate was 5% in both the treatment and placebo group without any significant differences in AKI or ARF[1]. Of note, the FDA issued a warning for other SGLT2 inhibitors (canagliflozin & dapagliflozin) for increased AKI/ARF risk in mid-2016[2].

A recent study investigated the short-term effects of torsemide with empagliflozin[3]. Compared to torsemide only, they found increased renin, aldosterone, and urinary volume levels in the combination group. Most importantly, patients lost 1.8kg on average in the combination group compared to 1.6kg and 0.4kg in the empagliflozin and torsemide only groups, respectively. There was a trend towards decreased creatinine clearance in the combination group however large variance was prohibitive of a significant difference. In addition, there was a trend towards lower SBPs in both groups without significant difference. Not surprisingly, thirst was reported in 60% of patients in the combination group, consistent with hypovolemia. Orthostatic hypotension, falls and hospitalizations were not reported.

The typical A1C goal of <7.0% is based on trials randomizing patients under the age of 60 with new or well controlled diabetes mellitus to intense or standard glycemic control. These studies determined intensive glucose control reduced the risk of microvascular outcomes after 8 years without reducing macrovascular events. Not surprisingly, the absolute risk of hypoglycemia increased by 5.4% (NNH 19) and 10.9% (NNH 10) in the VADT and ACCORD trials indicating that

tight control is not benign[4]. In line with risk reduction, the ADA advocates for an A1C goal of <8% in patients with "severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, or extensive comorbid conditions[5]." An A1C goal of 8% correlates with an average glucose of approximately 180 which is equivalent to renal reabsorption threshold. In this patient, a further liberalized A1C goal of <8.5% given his comorbidities and life expectancy would be acceptable in the absence of hyperglycemic symptoms including polyuria, fatigue, infection and cognitive impairment.

This patient likely experienced net harm as a result of starting an SGLT2 inhibitor. Although empagliflozin is well publicized for its beneficial cardiac effects, clinicians sometimes overlook the mechanism of action and the possible adverse events associated with osmotic diuresis. It is important to weigh the risks and benefits of starting an SGLT2 inhibitor in high fall risk patients on diuretics and individualize A1C goals with all patients.

References

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